Targeting mitochondrial calcium pathways as a potential treatment against Parkinson's disease

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Abstract: Parkinson's disease (PD) is a major health problem worldwide affecting millions of people and is a result of neurodegeneration in a small part of the brain known as substantia nigra pars compacta. Aberration in mitochondrial Ca2+ homeostasis plays, among several other factors, an important role for the neuronal loss in PD. Mitochondria are vital for cellular physiology, e.g. for ATP generation, and mitochondrial Ca2+ is a key player in cell functioning and survival. Mitochondrial Ca2+ homeostasis is maintained by a fine balance between the activities of proteins mediating the influx and efflux of Ca2+ across mitochondrial membranes. Malfunctioning of these proteins leading to Ca2+ overload promotes ROS generation, which induces cell death by triggering the opening of mitochondrial permeability transition pore. Till now PD remains incurable and the "gold standard" drug which can only delays the disease progression is l-Dopa from the 1960s and therefore, the situation warrants the search for novel targets for the treatment of the PD patients. In this review, we summarize the current views that suggest mitochondrial Ca2+ regulatory pathways are good candidates for the treatment of PD.

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Targeting mitochondrial calcium pathways as a potential treatment against Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a major health problem worldwide affecting millions of people and is a result of neurodegeneration in a small part of the brain known as *substantia nigra pars compacta*. Aberration in mitochondrial Ca^{2+} homeostasis plays, among several other factors, an important role for the neuronal loss in PD. Mitochondria are vital for cellular physiology, e.g. for ATP generation, and mitochondrial Ca^{2+} is a key player in cell functioning and survival. Mitochondrial Ca^{2+} homeostasis is maintained by a fine balance between the activities of proteins mediating the influx and efflux of Ca^{2+} across mitochondrial membranes. Malfunctioning of these proteins leading to Ca^{2+} overload promotes ROS generation, which induces cell death by triggering the opening of mitochondrial permeability transition pore. Till now PD remains incurable and the "gold standard" drug which can only delays the disease progression is L-Dopa from the 1960s and therefore, the situation warrants the search for novel targets for the treatment of the PD patients. In this review, we summarize the current views that suggest mitochondrial Ca^{2+} regulatory pathways are good candidates for the treatment of PD.

1. Introduction

Neurological, mental, and behavioral diseases are common in all countries and affect millions of people worldwide. Importantly, there are no effective treatments for many of these disorders. To develop the strategies and efficient drugs to stop them or at least to delay their progress, more basic research is needed. Two major neurodegenerative disorders are Alzheimer's disease (AD) and Parkinson's disease (PD) affecting about 50 and 6 million people around the world, respectively. These numbers will likely increase because of aging of the world's population. Age is a major risk factor in AD and PD, however, the environmental factors might also contribute to pathogenesis.

Major parts of the brain such as entorhinal cortex and hippocampus are affected in AD, whereas PD results from neurodegeneration process in a small and defined area of the brain called *substantia nigra pars compacta* (SNpc). This region in the midbrain is involved in movement control and contains dopaminergic neurons (DNs), which degenerate during the progress of the disease. Dopaminergic cell loss is one of two primary criteria for the diagnosis of PD [1]. The etiology of PD involves multiple factors, including genetic and environmental ones. For instance, a compound called 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produces a rapid onset of parkinsonian syndrome associated with a degeneration of DNs. Some factors such as caffeine or anti-inflammatory drugs may play a protective role by reducing the risk of developing PD.

Mutations in six genes such as α-SNCA, ATP13A2, DJ-1, LRRK2, Parkin, and PINK1 are known to cause the familial PD [2]. Remarkably, in different PD versions there is an apparent intracellular Ca^{2+} dysregulation, e.g. loss of function of PINK1 gene leads to Ca^{2+} mishandling [3–6]. Considering that in neurons, many reactions are regulated by Ca^{2+}, it is understandable that Ca^{2+} signaling is fundamentally important for proper neuronal functions and survival [7]. Global changes in Ca^{2+} homeostasis accompanied by the alteration in the bioenergetic status and thereby imposing oxidative stress on the cells are reported in PD [8,9]. For example, α-Synuclein, a 140-amino acid residues cytosolic protein involved in the pathogenesis of PD, was reported to form α-helical channels in the plasma membrane and allow extracellular Ca^{2+} transfer and thereby increases cytosolic Ca^{2+} concentration [9,10]. Additionally, recent research revealed the presence of α-Synuclein in mitochondria as well as in mitochondria associated ER

Abbreviations: AD, Alzheimer's disease; IMS, intermembrane space; M, mitochondrial matrix; MCU, mitochondrial calcium uniporter; MPTP, chemical specifically toxic to dopaminergic neurons; mPTP, mitochondrial permeability transition pore; NCLX, mitochondrial Na^+/Ca^{2+} exchanger; PINK1, PTEN-induced kinase 1; OMM, outer mitochondrial membrane; PD, Parkinson's Disease; RyR, Ryanodine receptor; VDAC, Voltage dependent anion channel

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membrane [11,12]. Interestingly, Paillusson et al. demonstrated that α-synuclein induced loosening of ER–mitochondria contacts disrupt Ca^{2+} exchange between these two organelles and thereby strongly affect PD phenotype [13]. Likewise, an enhanced activity of L-type Ca^{2+} channels leading to increased cytosolic Ca^{2+} influx has been shown in PD [14]. Enhanced cytosolic Ca^{2+} concentration, on the other hand, affects the bioenergetics of the cells by promoting a higher ATP demand [9]. Moreover, this alteration in cytosolic Ca^{2+} hampers the normal Ca^{2+} handling by various intracellular organelles and thus threatens neuronal viability [4–6,15]. Cytosolic Ca^{2+} is sequestered into different cellular organelles such as endoplasmic reticulum, mitochondria, Golgi, and lysosomes [16–20]. There are extensive evidences for the functional involvement of mitochondria, in particular mitochondrial oxidative stress, in PD [21,22]. Interestingly, inhibiting mitochondrial Ca^{2+} uptake diminishes the oxidative stress in SNpc DNs indicating that mitochondrial oxidative stress may also be the consequence of mitochondrial Ca^{2+} overload and not only for the need of enhanced ATP production [23].

Despite long-lasting efforts PD is still incurable. However, there are treatments which can improve the quality of life of the patients. The use of compound L-DOPA, a dopamine precursor which easily crosses blood-brain barrier, as a treatment for PD was introduced in the sixties and it still remains the pharmacological "gold standard" approach [24]. During recent years many therapies were evaluated to improve symptoms in PD. The list of these compounds includes rasagiline, amantadine, pramipexole, ropinirole [24], and selegiline [25]. Isradipine, a dihydropyridine Ca^{2+} channel antagonist (interacts with $Ca_V1.2$ and $Ca_V1.3$ channels in the hippocampus) was shown to be neuroprotective in *in vitro and in vivo* Parkinson models [26,27]. A phase III trial is going on to evaluate the efficacy of isradipine to slow the progression of disability in early PD [28]. Isradipine will be an attractive choice in the PD treatment because this drug easily crosses the blood-brain barrier and is already approved for the treatment of high blood pressure [25,26]. This is an exciting development since in another clinical trial, focused on related field of NMDA receptor-based stroke treatments (glutamate-induced excitotoxicity) have failed due to many side effects [29,30]. However, a lot of questions remain to be answered regarding the beneficial effect and thus the use of isradipine in PD pathology. For example, what is the mechanism responsible for the beneficial inhibition of the plasma membrane Ca^{2+} channels? Does isradipine treatment reduces mitochondrial Ca^{2+} overload and thus acts as a neuroprotective agent? It has already been pointed out that mitochondrial and neuronal dysfunction in PD is caused by mitochondrial calcium influx [6]. This indicated that Pink1 has an important function in regulating mitochondrial activity under stress conditions. Recent research from our group support their observations and indicated that knocking out Mcu, which leads to a blockade of Ca^{2+} entrance to the mitochondrial matrix, rescues the loss of dopaminergic neurons in Pink1 mutant of *Danio rerio* [31]. Therefore, in this review we are exploring whether it would be possible to target mitochondrial Ca^{2+} regulatory components in PD pathology. In the subsequent sections, we will first scrutinize the role of the candidate proteins responsible for mitochondrial Ca^{2+} transport and then we will discuss mitochondrial Ca^{2+} flow pathways as potential drug targets for PD therapy.

2. Calcium in mitochondria

Ca^{2+} inside the mitochondria regulates different processes that are crucial for cell functioning. These ions are involved in energy production (ATP), opening of the mitochondrial permeability transition pore (mPTP) and both triggering and preventing apoptosis [32]. There are several potential entry and exit sites for Ca^{2+} in mitochondria, and key players were depicted on the Fig. 1. Ca^{2+} concentration in mitochondria depends on the routes sprawling across ER, mitochondrion-associated membranes (MAMs) and mitochondria [33,34].

Two major channels that mediate Ca^{2+} influx into mitochondria are

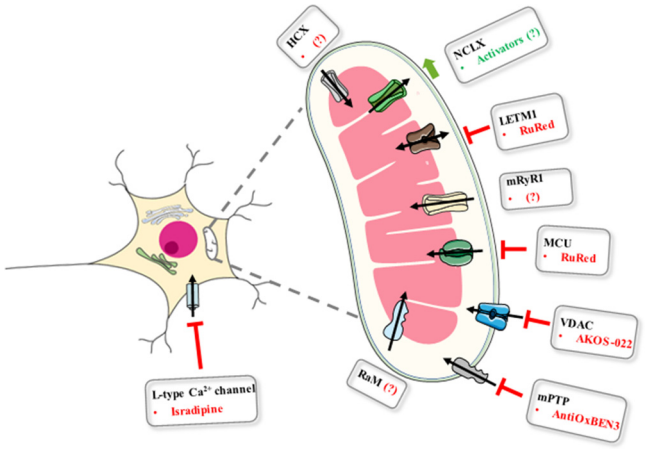

Fig. 1. Possible Ca^{2+} transporters with proven or potential pharmacological modulators for the treatment of Parkinson's disease. For the modulators, only one example is presented herein. For details consult Table 1.

(i) Voltage dependent anion channel (VDAC) and (ii) the mitochondrial calcium uniporter (MCU) [35–41]. VDAC is located in the outer mitochondrial membrane (OMM) and is responsible for the transport of Ca^{2+} to the inter-membrane space (IMS). Till now three different isoforms of VDAC have been identified, VDAC1, VDAC2 and VDAC3. Among them VDAC1 has been best studied, whereas only a limited information is available for VDAC2 or VDAC3 [42]. VDAC1, being highly Ca^{2+}-permeable, permits Ca^{2+} into and out of the mitochondria thereby affecting various cellular processes [43–46]. Importantly, VDAC1 functions in the junction between mitochondria and ER to facilitate the passage of Ca^{2+} from ER to mitochondria and regulate the apoptotic cell death pathways [47,48].

Ca^{2+} movement from the IMS to the mitochondrial matrix is mediated by MCU, which is located in the inner-mitochondrial membrane (IMM) and have low Ca^{2+} affinity. Mitochondrial matrix Ca^{2+} ($[Ca^{2+}]m$) level is almost equal to that of cytoplasm (~100 nM) under resting conditions and therefore MCU is inactive despite the driving force of the mitochondrial transmembrane potential ($\Delta\Psi(m)$), which is produced by the respiratory chain. However, upon stimulation when the cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]c$) rises rapidly (to 500–800 nM or even higher in some cells [49]), the MCU becomes active and passes Ca^{2+} into mitochondria instantaneously [38,49–51]. The MCU activity is manipulated by its regulatory proteins [52], which altogether form a heteromeric complex. The components of the MCU heteromeric complex includes mitochondrial calcium uptake (MICU1, MICU2 and MICU3), MCU dominant negative beta subunit (MCUb), essential MCU regulator (EMRE), MCU regulator 1 (MCUR1) and SLC25A23. Although MCU is expressed ubiquitously, the expression patterns of its regulatory proteins are tissue specific [53]. An interesting structure-function relationship exists between MCU and its regulators in order to manipulate the activity of MCU [52]. MICU1 works as a vital gatekeeper of MCU and inhibits its activity. Later on, it was found that MICU2 interacts with MICU1 in its inhibitory, gatekeeper role to keep the channel closed below a certain Ca^{2+} threshold [49]. MCUR1 and MCUb directly bind to MCU exerting a positive and dominant negative effect on MCU activity, respectively [51,54,55]. The other protein EMRE is required for the interaction of MCU with MICU1 and MICU2 [56]. At low cytosolic Ca^{2+} level MICU2 inhibits MCU activity by binding with MICU1. When cytosolic Ca^{2+} level increases MICU1-MICU2 dimer dissociates from the heteromeric complex and therefore, loses its inhibitory activity, and ultimately Ca^{2+} flows from cytosol into mitochondria through MCU [52].

A recent article from our group showed that (a) mitochondria that were isolated from *mcu*$^{-/-}$ zebrafish were unable to absorb Ca^{2+} from the medium and (b) those fish were viable, fertile and lacked gross

morphological aberrations [31]. A similar outcome was found in the previous mice study by Pan et al. [57]. These observations support earlier report by Marongiu et al. [6] that blockage of mitochondrial calcium influx completely rescues mitochondria from damage induced by mutant Pink1. Likewise, the knockout of *Mcu* in mice on a CD1 background was not lethal and had a weak phenotype, which suggests the existence of additional entry routes to mitochondria [58]. If this unrecognized entry route exists in mitochondria, it may require the activity of channels or other proteins that reside in the ER and/or PM [38,40]. One such pathway might involve rapid uptake mode (RaM) [59], but its molecular identity has not yet been defined. Another pathway might be mitochondrial ryanodine receptor (RyR) that is expressed at high levels in neurons [38,60] or channel that consists of LETM1 (leucine zipper- EF- hand containing transmembrane protein 1) [61–64]. LETM1 is a high affinity mitochondrial Ca^{2+}/H^{+} exchanger [61,63], and is able to drive both extrusion and uptake of Ca^{2+} into energized mitochondria at submicromolar Ca^{2+} concentrations. LETM1 has been shown to maintain the mitochondrial tubular shape [65]. However, debates continue regarding its role in Ca^{2+} extrusion [61,66].

There are still other candidates, which could be responsible for Ca^{2+} influx inside the mitochondria, e.g. (i) UCP2 [67] and UCP3 (BMCP1), which are highly expressed in the brain [68], (iii) proteins that belong to the family of TMBIM membrane proteins, such as TMBIM (called also GHITM, MICS1, or DERP2) [69], (iv) potential channel proteins that are listed in MitoCarta, but do not have an assigned function [70].

Ca^{2+} efflux from the mitochondrial matrix to IMS is a necessity for the cells in order to maintain resting Ca^{2+} level inside the mitochondria. This efflux is mediated by a well-known mitochondrial Na^{+}/Ca^{2+} exchanger, NCLX (encoded by the *SLC8B1* gene) importing 3 Na^{+} in exchange of 1 Ca^{2+} [4,71]. NCLX is different from plasma membrane NCX with respect to its sensitivity towards Li^{+}. A recent study from Roy et al. provide functional insights into the unique selectivity for Li^{+} and Na^{+} of the mitochondrial exchanger [71]. They identified distinct Na^{+} and Li^{+} selective residues in the NCLX transport site and propose that functional segregation in Li^{+} and Na^{+} sites reflects the functional properties of NCLX required for Ca^{2+} exchange under the unique membrane potential and ion gradient across the inner mitochondrial membrane.

Another mechanism for Ca^{2+} release from mitochondria is through the transient opening of mPTP, the molecular composition of which is yet undefined. It is proposed that mPTP is composed of several different protein components such as VDAC1 (in the OMM), ANT (in the IMM), F0F1-ATP synthase [38,72], and cyclophilin D in the matrix [73–75]. Nevertheless, its function is probably related to Ca^{2+} overload that depolarizes mitochondria leading to activation of different cell pathways associated with pathophysiological conditions [74–76].

3. Mitochondrial Ca^{2+} pathways as targets of anti-PD treatment

It has been reviewed that crosstalk between different mitochondrial proteins is involved in several physiological and pathophysiological conditions [77]. Ca^{2+} uptake into the mitochondrial matrix helps to maintain normal synaptic activity via enhanced respiratory function [78,79]. However, enhanced or sustained Ca^{2+} stress results in mitochondrial injury due to Ca^{2+} overload. Excess mitochondrial Ca^{2+} uptake or impaired Ca^{2+} efflux results in ROS production [80,81], breakdown of membrane potential and opening of the mPTP, and therefore induction of neuronal cell death, an important indicator of several different neurological disorders including AD and PD. Our group explored the mechanisms of early onset PD of genetic origin by using zebrafish with mutation in *pink1* gene, which exhibits loss of about 20% of DNs already at 5 days post fertilization (dpf) [3,31]. Dysregulation of Ca^{2+} transport into mitochondria seems to be an early molecular mechanism of the pathology [47,82–86]. We found that both a morpholino against *mcu* and its pharmacological inhibition by Ruthenium Red rescued the loss of dopaminergic neurons in *pink1*$^{-/-}$ zebrafish [3]. A subsequent study confirmed the role of Mcu in rescuing the neuronal loss by using a double mutant zebrafish (*pink1;mcu*)$^{-/-}$ model [31]. This data shows that in Pink1-PD model the lack of Mcu rescues the pathology. We also showed that the absence of Mcu made the fish resistant to **M**PTP, a drug that kills dopaminergic neurons, and often used to make models of PD [24]. Very recently, Marco et al. [87] claimed that inhibition of MICU1 activity by two newly identified pharmacological inhibitors namely MCU-i4 and MCU-i11 can prevent mitochondrial Ca^{2+} overload. A similar outcome was observed in LRRK2-PD model with increased intracellular Ca^{2+} uptake, which results in enhanced mitophagy and thus mitochondrial loss [88]. The treatment with VDAC inhibitors rescued the neurons from mitophagic death, again indicating the importance of Ca^{2+} uptake in controlling the neuronal cell fate [88].

While different studies implicated MCU in the PD pathology, studies of others suggested that pharmacological inhibition of NCLX with CGP37157 was neuroprotective [5,89]. However, Ruiz et al. later showed that the neuroprotective effect of CGP37157 is not only through its inhibitory action on NCLX, but it also modulates cytosolic and mitochondrial Ca^{2+} dynamics via VGCCs [90]. Nevertheless, the work from Elrod group unravel the importance of NCLX in cell viability [81]. They demonstrated that animals with tamoxifen-induced deletion of NCLX gene died within several hours after gene deletion, which was associated with mitochondrial Ca^{2+} overload and induction of the mPTP pore. Alongside with this report, research from two different laboratories, by using PINK1 and LRRK2 PD models, provided evidences which demonstrated that NCLX plays an important role in PD pathology. Expression of a constitutively active mutant of NCLX, which enhances Ca^{2+} export from mitochondria has been shown to be neuroprotective in both PINK1 and LRRK2 PD model [4,91]. An interesting study from Hail et al. [92] showed that inhibition of VDAC1 oligomerization with AKOS-022 inhibits neuronal cell death and therefore might have an important impact on neuronal death in PD. Thus, all these studies support the view that the proper homeostasis of mitochondrial Ca^{2+} is crucial for well-being of the DNs. If so, anti-PD treatments should take into account the compounds that prevent mitochondrial Ca^{2+} overload.

What could be the drug for treating Ca^{2+} dependent mitochondrial malfunctions in PD? Below we propose some requirements for such a wonder drug and describe potential lead candidates. First, it should be specific to mitochondrial Ca^{2+} route, either by blocking influx of Ca^{2+} or enhancing its efflux. Second, it should be crossing blood-brain barrier and affecting preferentially dopaminergic neurons. Third, it cannot affect muscles and other neurons to avoid significant side effects. Its use will be recommended continuously since the early stages of the disease, like for instance, hypertension drugs.

To get the better picture of mechanisms responsible for Ca^{2+} transport in mitochondria, we gathered them in Table 1 and assigned to them known particles, that could be used as regulators, activators and inhibitors. Most of influx mechanism toward mitochondrial matrix can be blocked by Ruthenium Red or a couple of other chemicals. However, until now no therapies connected with these were introduced, mostly because of limited selectivity and efficacy. Yet, we think that pursuing this way is really worth, because, as it was mentioned above, genetically blocking Ca^{2+} overload in mitochondria via Mcu had the rescue effect in animal PD model. Alongside, chemical blocking of cell membrane L-type channels by Isradipine is very promising. Still these blockers are widely used to induce and stimulate controlled Ca^{2+} dysregulation in most of calcium field research. Recently a specific mPTP inhibitor – AntiOxBEN3 was developed, which may open a way to consecutive approach of chemical model of Ca^{2+} overload in the cell [93]. There are still some unknown fields for activators/inducers of mechanisms responsible for Ca^{2+} efflux from mitochondria. Would an induction of more efficient Ca^{2+} export be an effective counterbalance

Table 1
Known and proposed Ca^{2+} entries/exits into mitochondrial compartments (CYT-cytosol, IMS-intermembrane space, MX-mitochondrial matrix) and their chemical modulators.

Name	Direction of Ca^{2+} transport	Regulators	Activators	Inhibitors
Voltage Dependent Anion Channel (VDAC)	CYT IMS	NADH [94]		Phosphorothioate oligonucleotides [95], VBIT-4 and AKOS-022 (block oligomerization) [92], Diphenylamine-2-carboxilic acid, Cyathin-R [77]
Mitochondrial Calcium Uniporter (MCU)	IMS MX	MICU1, MICU2 MICU3 [49], MCUb [54], EMRE [56]	Polyamines [96], SB202190 [97], Flavonoids [98], PPT [99]	MCU-i4 & MCU-i11 (MICU1 inhibitors) [87], Inorganic Ruthenium complex [100], KB-R7943 [101]
Rapid uptake Mode (RaM)	IMS MX		Spermine and Spermadine [102] Taurine [103]	RuRed, Ru360 [59]
Mitochondrial Ryanodine Receptor1 (mRyR1)	IMS MX	Many [104]	Imperatoxine A [104]	RuRed, Ryanodine, Dantrolene [105,106]
Leucine zipper- EF- hand containing transmembrane protein 1 (Letm1)	IMS MX IMS			RuRed [62]
Mitochondrial Na^+ Ca^{2+} exchanger (NCLX)	MX IMS	Protein kinase A [4]		CGP37157 [90,105,107,108]
$Ca^{2+}/H^+/Na^+$ antiporters (HCX)	MX IMS			Diltiazem [109], Tetraphenylphosphonium [110]
Mitochondrial Permeability Transition Pore (mPTP)	IMS CYT	Many [111]	Atractyloside [112]	AntiOxBEN3 [93], CypD inhibitor Cyclosporine A [113], Bongkrekic acid [114]

to overload causing pathologies? Another option is to focus on the regulation mechanism of MCU, residing outside mitochondria – inside the MAMs and ER. These parts of the cell could be more specifically targeted and then it would influence the MCU efficiency.

4. Concluding remarks

Parkinson's disease is a neurodegenerative disorder, the actual cause of which remains unknown. However, growing understanding about mechanisms leading to PD phenotype have been accumulated which includes progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. The mechanisms behind the selective loss of DA neurons in the SNpc of PD patients is under active investigation. Nevertheless, studies using animal and cellular models based on familial form of PD or environmental factors (e.g. **M**PTP toxicity) is providing useful insights into the mechanisms of neurodegeneration of DA neurons. Importantly, changes in mitochondrial Ca^{2+} homeostasis are one of the prominent markers for the neuronal loss in PD pathology. Mitochondrial Ca^{2+} aids the bioenergetic status of the cell and thus fine tuning of the mitochondrial Ca^{2+} is essential for a cell. Malfunctioning of the mitochondrial Ca^{2+} transporters leading to Ca^{2+} overload causes mitochondrial membrane potential collapse, disintegration of mitochondria, release of pro apoptotic proteins and ultimately cell death. Therefore, targeting mitochondrial Ca^{2+} sensors and/or transporters represents an attractive therapeutic strategy in PD.

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References

[1] M. Toffoli, S.R.L. Vieira, A.H.V. Schapira, Genetic causes of PD: a pathway to disease modification, Neuropharmacology 170 (2020) 108022 [Epub ahead of print].
[2] D.K. Simon, C.M. Tanner, P. Brundin, Parkinson disease epidemiology, pathology, genetics, and pathophysiology, Clin. Geriatr. Med. 36 (2020) 1–12.
[3] S. Soman, M. Keatinge, M. Moein, et al., Inhibition of the mitochondrial calcium uniporter rescues dopaminergic neurons in pink1(-/-) zebrafish, Eur. J. Neurosci. 45 (2017) 528–535.
[4] M. Kostic, M.H.R. Ludtmann, H. Bading, et al., PKA phosphorylation of NCLX reverses mitochondrial calcium overload and depolarization, promoting survival of PINK1-Deficient dopaminergic neurons, Cell Rep. 13 (2015) 376–386.
[5] S. Gandhi, A. Wood-Kaczmar, Z. Yao, et al., PINK1-associated parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death, Mol. Cell 33 (2009) 627–638.
[6] R. Marongiu, B. Spencer, L. Crews, et al., Mutant Pink1 induces mitochondrial dysfunction in a neuronal cell model of Parkinson's disease by disturbing calcium flux, J. Neurochem. 108 (2009) 1561–1574.
[7] G.J. Augustine, F. Santamaria, K. Tanaka, Local calcium signaling in neurons, Neuron 40 (2003) 331–346.
[8] M.H.R. Ludtmann, A.Y. Abramov, Mitochondrial calcium imbalance in Parkinson's disease, Neurosci. Lett. 10 (2018) 86–90.
[9] D.J. Surmeier, P.T. Schumacker, Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease, J. Biol. Chem. 288 (2013) 10736–10741.
[10] S.D. Zakharov, J.D. Hulleman, E.A. Dutseva, Y.N. Antonenko, J.C. Rochet, W.A. Cramer, Helical alpha-synuclein forms highly conductive ion channels, Biochemistry 46 (2007) 14369–14379.
[11] M. Alloatti, M.B. Pardi, T.M. Saez, et al., αSynuclein control of mitochondrial homeostasis in human-derived neurons is disrupted by mutations associated with Parkinson's disease, Sci. Rep. 7 (2017) 5042 Pozo.
[12] C. Guardia-Laguarta, E. Area-Gomez, C. Rüb, et al., α-Synuclein is localized to mitochondria-associated ER membranes, J. Neurosci. 34 (2014) 249–259.
[13] S. Paillusson, P. Gomez-Suaga, R. Stoica, et al., α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production, Acta Neuropathol. 134 (2017) 129–149.
[14] C.S. Chan, J.N. Guzman, J.N.E. Ilijic, et al., 'ReJuvenation' protects neurons in mouse models of Parkinson's disease, Nature 447 (2007) 1081–1086.
[15] T. Calì, D. Ottolini, M. Brini, Mitochondria, calcium, and endoplasmic reticulum stress in Parkinson's disease, Biofactors 37 (2011) 228–240.
[16] R. Rizzuto, D. De Stefani, A. Raffaello, C. Mammucari, Mitochondria as sensors and regulators of calcium signalling, Nat. Rev. Mol. Cell Biol. 13 (2012) 566–578.
[17] S. Xue, M. Nicoud, J. Cui, et al., High concentration of calcium ions in Golgi

apparatus, Cell Res. 4 (1994) 97–108.
[18] P. Pizzo, V. Lissandron, P. Capitanio, T. Pozzan, Ca(2+) signalling in the Golgi apparatus, Cell Calc. 50 (2011) 184–192.
[19] X. Feng, J. Yang, Lysosomal calcium in neurodegeneration, Messenger (Los Angel) 5 (2016) 56–66.
[20] J. Krebs, L.B. Agellon, M. Michalak, Ca(2+) homeostasis and endoplasmic reticulum (ER) stress: an integrated view of calcium signaling, Biochem. Biophys. Res. Commun. 460 (2015) 114–121.
[21] P.M. Keeney, J. Xie, R.A. Capaldi, J.P. Bennett Jr., Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled, J. Neurosci. 26 (2006) 5256–5264.
[22] S.R. Subramaniam, M.F. Chesselet, Mitochondrial dysfunction and oxidative stress in Parkinson's disease, Prog. Neurobiol. 106–107 (2013) 17–32.
[23] J.N. Guzman, J. Sanchez-Padilla, D. Wokosin, J. Kondapalli, E. Ilijic, P.T. Schumacker, D.J. Surmeier, Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1, Nature 468 (2010) 696–700.
[24] P. Rizek, N. Kumar, M.S. Jog, An update on the diagnosis and treatment of Parkinson disease, CMAJ. 188 (2016) 1157–1165.
[25] G. Fabbrini, G. Abbruzzese, S. Marconi, M. Zappia, Selegiline: a reappraisal of its role in Parkinson disease, Clin. Neuropharmacol. 35 (2012) 134–140.
[26] J.N. Guzman, E. Ilijic, B. Yang, et al., Systemic isradipine treatment diminishes calcium-dependent mitochondrial oxidant stress, J. Clin. Invest. 128 (2018) 2266–2280.
[27] E. Ilijic, J.N. Guzman, D.J. Surmeier, The L-type channel antagonist isradipine is neuroprotective in a mouse model of Parkinson's disease, Neurobiol. Dis. 43 (2011) 364–371.
[28] T. Simuni, R. Holloway, D. Oakes, K. Biglan, C. Lungu, A Phase 3 study of Isradipine as a disease modifying agent in patients with early Parkinson's disease (STEADY-PD III): baseline characteristics and study update, Neurology P2.039 (2018) 90.
[29] B.C. Albensi, C. Igoechi, D. Janigro, E. Ilkanich, Why do many NMDA antagonists fail, while others are safe and effective at blocking excitotoxicity associated with dementia and acute injury? Am. J. Alzheimer's Dis. Other Dementias 19 (2004) 269–274.
[30] V. Li, Y. Wang, Molecular mechanisms of NMDA receptor-mediated excitotoxicity: implications for neuroprotective therapeutics for stroke, Neural Regen. Res. 11 (2016) 1752–1753.
[31] S.K. Soman, M. Bazała, M. Keatinge, O. Bandmann, J. Kuznicki, Restriction of mitochondrial calcium overload by mcu inactivation renders a neuroprotective effect in zebrafish models of Parkinson's disease, Biol. Open 8 (2019) bio044347.
[32] B. Wacquier, L. Combettes, G.T. Van Nhieu, Dupont G. Interplay between intracellular Ca^{2+} oscillations and Ca^{2+}-stimulated mitochondrial metabolism, Sci. Rep. 6 (2016) 19316.
[33] R. Rizzuto, $^{2+}$Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca responses, Science 280 (1998) 1763–1766.
[34] R. Rizzuto, T. Pozzan, Microdomains of intracellular Ca^{2+}: molecular determinants and functional consequences, Physiol. Rev. 86 (2006) 369–408.
[35] Z. Xu, D. Zhang, X. He, Y. Huang, H. Shao, Transport of calcium ions into mitochondria, Curr. Genomics 17 (2016) 215–219.
[36] D. De Stefani, A. Raffaello, E. Teardo, I. Szabò, R. Rizzuto, A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter, Nature 476 (2011) 336–340.
[37] D. De Stefani, M. Patron, R. Rizzuto, Structure and function of the mitochondrial calcium uniporter complex, Biochim. Biophys. Acta – Mol. Cell Res. 1853 (2015) 2006–2011.
[38] J.M. Baughman, F. Perocchi, H.S. Girgis, et al., Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter, Nature 476 (2011) 341.
[39] E. Penna, J. Espino, D. De Stefani, R. Rizzuto, The MCU complex in cell death, Cell Calc. 69 (2018) 73–80.
[40] D. Pendin, E. Greotti, T. Pozzan, The elusive importance of being a mitochondrial Ca^{2+} uniporter, Cell Calc. 55 (2014) 139–145.
[41] C. Mammucari, A. Raffaello, D. Vecellio Reane, R. Rizzuto, Molecular structure and pathophysiological roles of the Mitochondrial Calcium Uniporter, Biochim. Biophys. Acta – Mol. Cell Res. 1863 (2016) 2457–2464.
[42] V. Shoshan-Barmatz, Y. Krelin, A. Shteinfer-Kuzmine, VDAC1 functions in Ca^{2+} homeostasis and cell life and death in health and disease, Cell Calc. 69 (2018) 81–100.
[43] D. Gincel, H. Zaid, V. Shoshan-Barmatz, Calcium binding and translocation by the voltage-dependent anion channel: a possible regulatory mechanism in mitochondrial function, Biochem. J. 358 (2001) 147–155.
[44] E. Rapizzi, P. Pinton, G. Szabadkai, et al., Recombinant expression of the voltage-dependent anion channel enhances the transfer of Ca^{2+} microdomains to mitochondria, J. Cell Biol. 159 (2002) 613–624.
[45] W. Tan, Y.H. Loke, C.A. Stein, P. Miller, M. Colombini, Phosphorothioate oligonucleotides block the VDAC channel, Biophys. J. 93 (2007) 1184–1191.
[46] G. Báthori, G. Csordás, C. Garcia-Perez, E. Davies, G. Hajnóczky, Ca^{2+}-dependent control of the permeability properties of the mitochondrial outer membrane and voltage-dependent anion-selective channel (VDAC), J. Biol. Chem. 281 (2006) 17347–17358.
[47] M. Müller, U. Ahumada-Castro, M. Sanhueza, C. Gonzalez-Billault, F.A. Court, C. Cárdenas, Mitochondria and calcium regulation as basis of neurodegeneration associated with aging, Front. Neurosci. 12 (2018) 470.
[48] S. Lee, K.T. Min, The interface between ER and mitochondria: molecular compositions and functions, Mol. Cells 41 (2018) 1000–1007.
[49] K.J. Kamer, Z. Grabarek, VK Mootha. High-affinity cooperative Ca^{2+} binding by MICU1-MICU2 serves as an on-off switch for the uniporter, EMBO Rep. 18 (2017) 1397–1411.
[50] D. Chaudhuri, Y. Sancak, V.K. Mootha, D.E. Clapham, MCU encodes the pore conducting mitochondrial calcium currents, Elife. 2 (2013) e00704.
[51] S. Marchi, P. Pinton, The mitochondrial calcium uniporter complex: molecular components, structure and physiopathological implications, J. Physiol. 592 (2014) 829–839.
[52] N. Nemani, S. Shanmughapriya, M. Madesh, Molecular regulation of MCU: implications in physiology and disease, Cell Calc. 74 (2018) 86–93.
[53] C. Fecher, L. Trovò, S.A. Müller, et al., Cell-type-specific profiling of brain mitochondria reveals functional and molecular diversity, Nat. Neurosci. 22 (2019) 1731–1742.
[54] K. Mallilankaraman, C. Cardenas, P.J. Doonan, et al., MCUR1 is an essential component of mitochondrial Ca^{2+} uptake that regulates cellular metabolism, Nat. Cell Biol. 14 (2012) 1336–1343.
[55] A. Raffaello, D. De Stefani, D. Sabbadin, et al., The mitochondrial calcium uniporter is a multimer that can include a dominant-negative pore-forming subunit, EMBO J. 32 (2013) 2362–2376.
[56] Y. Sancak, A.L. Markhard, T. Kitami, T, EMRE is an essential component of the mitochondrial calcium uniporter complex, Science 342 (2013) 1379–1382.
[57] X. Pan, J. Liu, T. Nguyen, et al., The physiological role of mitochondrial calcium revealed by mice lacking the mitochondrial calcium uniporter, Nat. Cell Biol. 15 (2013) 1464–1472.
[58] E. Murphy, X. Pan, T. Nguyen, J. Liu, K.M. Holmström, T. Finkel, Unresolved questions from the analysis of mice lacking MCU expression, Biochem. Biophys. Res. Commun. 449 (2014) 384–385.
[59] G.C. Sparagna, K.K. Gunter, T.E. Gunter, A system for producing and monitoring in vitro calcium pulses similar to those observed in vivo, Anal. Biochem. 219 (1994) 96–103.
[60] R. Jakob, G. Beutner, V.K. Sharma, et al., Molecular and functional identification of a mitochondrial ryanodine receptor in neurons, Neurosci. Lett. 575 (2014) 7–12.
[61] D. Jiang, L. Zhao, D.E. Clapham, Genome wide RNAi screen identifies Letm1 as a mitochondrial Ca^{2+}/H^{+} antiporter, Science 326 (2009) 144–147.
[62] E. Huang, D. Qu, T. Huang, et al., PINK1-mediated phosphorylation of LETM1 regulates mitochondrial calcium transport and protects neurons against mitochondrial stress, Nat. Commun. 8 (2017) 1399.
[63] K. Nowikovsky, T. Pozzan, R. Rizzuto, L. Scorrano, P. Bernardi, The pathophysiology of LETM1, J. Gen. Physiol. 139 (2012) 445–454.
[64] S.-Y. Lee, M.-G. Kang, S. Shin, et al., Architecture mapping of the inner mitochondrial membrane proteome by chemical tools in live cells, J. Am. Chem. Soc. 139 (2017) 3651–3662.
[65] S. Tamai, H. Iida, S. Yokota, et al., Characterization of the mitochondrial protein LETM1, which maintains the mitochondrial tubular shapes and interacts with the AAA-ATPase BCS1L, J. Cell. Sci. 121 (2008) 2588–2600.
[66] U. De Marchi, J. Santo-Domingo, C. Castelbou, I. Sekler, A. Wiederkehr, N. Demaurex, NCLX protein, but not LETM1, mediates mitochondrial Ca^{2+} extrusion, thereby limiting Ca^{2+}-induced NAD(P)H production and modulating matrix redox state, J. Biol. Chem. 289 (2014) 20377–20385.
[67] C. Toda, S. Diano, Mitochondrial UCP2 in the central regulation of metabolism, Best Pract. Res. Clin. Endocrinol. Metab. 28 (2014) 757–764.
[68] T. Hoang, M.D. Smith, M. Jelokhani-Niaraki, Toward understanding the mechanism of ion transport activity of neuronal uncoupling proteins UCP2, UCP4, and UCP5, Biochemistry. 51 (2012) 4004–4014.
[69] Q. Liu, TMBIM-mediated Ca^{2+} homeostasis and cell death, Biochim. Biophys. Acta – Mol. Cell Res. 1864 (2017) 850–857.
[70] D.J. Pagliarini, S.E. Calvo, B. Chang, et al., A mitochondrial protein compendium elucidates complex I disease biology, Cell 134 (2008) 112–123.
[71] S. Roy, K. Dey, M. Hershfinkel, E. Ohana, I. Sekler, Identification of residues that control Li^{+} versus Na^{+} dependent Ca^{2+} exchange at the transport site of the mitochondrial NCLX, Biochim. Biophys. Acta – Mol. Cell Res. 1864 (2017) 997–1008.
[72] V. Giorgio, S. von Stockum, M. Antoniel, et al., Dimers of mitochondrial ATP synthase form the permeability transition pore, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 5887–5892.
[73] J.W. Elrod, R. Wong, S. Mishra, et al., Cyclophilin D controls mitochondrial pore-dependent Ca^{2+} exchange, metabolic flexibility, and propensity for heart failure in mice, J. Clin. Invest. 120 (2010) 3680–3687.
[74] Y. Tsujimoto, S. Shimizu, Role of the mitochondrial membrane permeability transition in cell death, Apoptosis 12 (2007) 835–840.
[75] V. Shoshan-Barmatz, D. Gincel, The voltage-dependent anion channel: characterization, modulation, and role in mitochondrial function in cell life and death, Cell Biochem. Biophys. 39 (2003) 279–292.
[76] A. Rasola, P. Bernardi, Mitochondrial permeability transition in Ca^{2+}-dependent apoptosis and necrosis, Cell Calc. 50 (2011) 222–233.
[77] V. Shoshan-Barmatz, S. De, A. Meir, $^{2+}$The mitochondrial voltage-dependent anion channel 1, Ca transport, apoptosis, and their regulation, Front. Oncol. 7 (2017) 60.
[78] K. Bianchi, A. Rimessi, A. Prandini, G. Szabadkai, R. Rizzuto, Calcium and mitochondria: mechanisms and functions of a troubled relationship, Biochim. Biophys. Acta 1742 (2004) 119–131.
[79] M. Vos, E. Lauwers, P. Verstreken, Synaptic mitochondria in synaptic transmission and organization of vesicle pools in health and disease, Front. Synaptic Neurosci. 2 (2010) 139.
[80] I.J. Reynolds, T.G. Hastings, Glutamate induces the production of reactive oxygen species in cultured forebrain neurons following NMDA receptor activation, J.

Neurosci. 15 (1995) 3318–3327.
[81] T.S. Luongo, J.P. Lambert, P. Gross, et al., The mitochondrial Na^+/Ca^{2+} exchanger is essential for Ca^{2+} homeostasis and viability, Nature 545 (2017) 93–97.
[82] S.V. Zaichick, K.M. McGrath, G. Caraveo, The role of Ca^{2+} signaling in Parkinson's disease, Dis. Model. Mech. 10 (2017) 519–535.
[83] M. Krols, G. van Isterdael, B. Asselbergh, et al., Mitochondria-associated membranes as hubs for neurodegeneration, Acta Neuropathol. 131 (2016) 505–523.
[84] E.M. Lynes, T. Simmen, Urban planning of the endoplasmic reticulum (ER): how diverse mechanisms segregate the many functions of the ER, Biochim. Biophys. Acta – Mol. Cell Res. 1813 (2011) 1893–1905.
[85] A. Bononi, S. Missiroli, F. Poletti, et al., Mitochondria-associated membranes (MAMs) as hotspot Ca(2+) signaling units, Adv. Exp. Med. Biol. 740 (2012) 411–437.
[86] C. Giorgi, S. Missiroli, S. Patergnani, J. Duszynski, M.R. Wieckowski, P. Pinton, Mitochondria-associated membranes: composition, molecular mechanisms, and physiopathological implications, Antioxid. Redox Signal. 22 (2015) 995–1019.
[87] G. Di Marco, F. Vallese, B. Jourde, et al., A high-throughput screening identifies MICU1 targeting compounds, Cell Rep. 30 (2020) 2321–2331.
[88] M. Verma, Z. Wills, C.T. Chu, Excitatory dendritic mitochondrial calcium toxicity: implications for parkinson's and other neurodegenerative diseases, Front. Neurosci. 12 (2018) 523.
[89] S.M. Nicolau, J. Egea, M.G. López, A.G. García, Mitochondrial Na+/Ca2+ exchanger, a new target for neuroprotection in rat hippocampal slices, Biochem. Biophys. Res. Commun. 400 (2010) 140–144.
[90] A. Ruiz, E. Alberdi, C. Matute, CGP37157, an inhibitor of the mitochondrial Na^+/Ca^{2+} exchanger, protects neurons from excitotoxicity by blocking voltage-gated Ca^{2+} channels, Cell Death Dis. 5 (2014) e1156.
[91] M.H.R. Ludtmann, M. Kostic, A. Horne, S. Gandhi, I. Sekler, A.Y. Abramov, LRRK2 deficiency induced mitochondrial Ca^{2+} efflux inhibition can be rescued by $Na^+/Ca^{2+}/Li^+$ exchanger upregulation, Cell Death Dis. 10 (2019) 265.
[92] D. Ben-Hail, R. Begas-Shvartz, M. Shalev, et al., Novel compounds targeting the mitochondrial protein VDAC1 inhibit apoptosis and protect against mitochondrial dysfunction, J. Biol. Chem. 291 (2016) 24986–25003.
[93] J. Teixeira, C. Oliveira, F. Cagide, R. Amorim, J. Garrido, F. Borges, P.J. Oliveira, Discovery of a new mitochondria permeability transition pore (mPTP) inhibitor based on gallic acid, J. Enzyme Inhib. Med. Chem. 33 (2018) 567–576.
[94] M. Zizi, M. Forte, E. Blachly-Dyson, M. Colombini, NADH regulates the gating of VDAC, the mitochondrial outer membrane channel, J. Biol. Chem. 269 (1994) 1614–1616.
[95] C.A. Stein, M. Colombini, Specific VDAC inhibitors: phosphorothioate oligonucleotides, J. Bioenerg. Biomembr. 40 (2008) 157–162.
[96] M. Salvi, A. Toninello, Effects of polyamines on mitochondrial Ca^{2+} transport, Biochim. Biophys. Acta Biomembr. 661 (2004) 113–124.
[97] M. Montero, C.D. Lobaton, A. Moreno, J. Alvarez, A novel regulatory mechanism of the mitochondrial Ca^{2+} uniporter revealed by the p38 mitogen-activated protein kinase inhibitor SB202190, FASEB J. 16 (2002) 1955–1957.
[98] M. Montero, C.D. Lobatón, E. Hernández-Sanmiguel, J. Santodomingo, L. Vay, A. Moreno, J. Alvarez, Biochem. J. 384 (2004) 19–24.
[99] C.D. Lobatón, L. Vay, E. Hernández-Sanmiguel, J. Santodomingo, A. Moreno, M. Montero, J. Alvarez, Modulation of mitochondrial Ca^{2+} uptake by estrogen receptor agonists and antagonists, Br. J. Pharmacol. 145 (2005) 862–871.
[100] J.J. Woods, N. Nemani, S. Shanmughapriya, et al., A selective and cell-permeable mitochondrial calcium uniporter (MCU) inhibitor preserves mitochondrial bioenergetics after Hypoxia/Reoxygenation injury, ACS Cent. Sci. 5 (2019) 153–166.
[101] J. Santo-Domingo, L. Vay, E. Hernández-Sanmiguel, C.D. Lobatón, A. Moreno, M. Montero, J. Alvarez, The plasma membrane Na^+/Ca^{2+} exchange inhibitor KB-R7943 is also a potent inhibitor of the mitochondrial Ca^{2+} uniporter, Br. J. Pharmacol. 151 (2007) 647–654.
[102] C.V. Nicchitta, J.R. Williamson, Spermine. A regulator of mitochondrial calcium cycling, J. Biol. Chem. 259 (1984) 12978–12983.
[103] M. Palmi, G.T. Youmbi, F. Fusi, G.P. Sgaragli, H.B. Dixon, M. Frosini, K.F. Tipton, Potentiation of mitochondrial Ca^{2+} sequestration by taurine, Biochem. Pharmacol. 58 (1999) 1123–1131.
[104] B.A. Altschafl, G. Beutner, V.K. Sharma, S.-S. Sheu, H.H. Valdivia, The mitochondrial ryanodine receptor in rat heart: a pharmaco-kinetic profile, Biochim. Biophys. Acta Biomembr. 1768 (2007) 1784– 95.
[105] J.H. Bae, J.W. Park, T.K. Kwon, Ruthenium red, inhibitor of mitochondrial Ca^{2+} uniporter, inhibits curcumin-induced apoptosis via the prevention of intracellular Ca^{2+} depletion and cytochrome c release, Biochem. Biophys. Res. Commun. 303 (2003) 1073–1079.
[106] G. Beutner, V.K. Sharma, D.R. Giovannucci, D.I. Yule, S.-S. Sheu, Identification of a ryanodine receptor in rat heart mitochondria, J. Biol. Chem. 276 (2001) 21482–21488.
[107] L. Boyman, G.S.B. Williams, D. Khananshvili, I. Sekler, W.J. Lederer, NCLX: the mitochondrial sodium calcium exchanger, J. Mol. Cell. Cardiol. 59 (2013) 205–213.
[108] Cox DA, M.A. Matlib, A role for the mitochondrial Na^+-Ca^{2+} exchanger in the regulation of oxidative phosphorylation in isolated heart mitochondria, J. Biol. Chem. 268 (1993) 938–947.
[109] R. Rizzuto, P. Bernardi, M. Favaron, G.F. Azzone, Pathways for Ca^{2+} efflux in heart and liver mitochondria, Biochem. J. 246 (1987) 271 LP-277.
[110] D.E. Wingrove, T.E. Gunter, Kinetics of mitochondrial calcium transport. II. A kinetic description of the sodium-dependent calcium efflux mechanism of liver mitochondria and inhibition by ruthenium red and by tetraphenylphosphonium, J. Biol. Chem. 261 (1986) 15166–15171.
[111] V.K. Rao, E.A. Carlson, S.S. Yan, Mitochondrial permeability transition pore is a potential drug target for neurodegeneration, Biochim. Biophys. Acta – Mol. Basis Dis. 1842 (2014) 1267–1272.
[112] Y.Y. Li, L. Xiao, L.Y. Qiu, et al., Sasanquasaponin-induced cardioprotection involves inhibition of mPTP opening via attenuating intracellular chloride accumulation, Fitoterapia 116 (2017) 1–9.
[113] K.M. Broekemeier, M.E. Dempsey, D.R. Pfeiffer, Cyclosporin A is a potent inhibitor of the inner membrane permeability transition in liver mitochondria, J. Biol. Chem. 264 (1989) 7826–7830.
[114] C.A. Gautier, E. Giaime, E. Caballero, et al., Regulation of mitochondrial permeability transition pore by PINK1, Mol. Neurodegener. 7 (2012) 22.